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(12) **UK Patent Application** (19) **GB** (11) **2 284 760** (13) **A**

(43) Date of A Publication 21.06.1995

<p>(21) Application No 9324045.5</p> <p>(22) Date of Filing 23.11.1993</p>	<p>(51) INT CL⁶ A61K 9/16 9/52</p>
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(54) **Sustained release morphine compositions**

(57) An orally administered sustained release dosage unit form containing morphine, or a pharmaceutically acceptable salt thereof, as active ingredient, which composition gives a peak plasma level at from 1.0 to 6 hours after administration. The morphine dosage form is suitable for once-a-day administration. It is preferably in the form of a capsule filled with pellets comprising morphine and a hydrophobic release control material such as a natural or synthetic wax or oil e.g. hydrogenated vegetable or castor oil.

A process for the manufacture of pellets comprises mechanically working a mixture of a drug and a hydrophobic fusible carrier in a high speed mixture so as to form agglomerates, breaking the agglomerates to give controlled release seeds and continuing the mechanical working with the addition of a low percentage of the carrier or diluent.

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SUSTAINED RELEASE COMPOSITIONS AND A METHOD OF
PREPARING PHARMACEUTICAL COMPOSITIONS

This invention is concerned with improvements in and relating to sustained release compositions and, more particularly, is concerned with sustained release orally administrable dosage unit forms containing morphine, or a pharmaceutically acceptable salt thereof, as active ingredient.

The present invention also relates generally to a method of manufacturing an orally administrable dosage form, preferably sustained release granules/pellets, such pellets having diameters ranging from 0.1 to 3.0mm; the method of the invention provides pellets in an unexpectedly considerably higher yield than melt pelletisation processes hitherto know. Such pellets may contain morphine or other active ingredients.

Morphine is an opioid analgesic well established for use in the treatment of pain, especially moderate to severe pain. Morphine-containing compositions in sustained release form are currently commercially available as so-called "twice-a-day" formulations, that is formulations having a duration of activity of 12 hours or more and accordingly requiring to be administered twice a day.

It is one object of the present invention to provide a morphine-containing sustained release orally administrable dosage unit form which has an effective duration of activity of 24 hours or more and, hence, is suitable for administration on a once daily basis.

It has surprisingly been found, in accordance with the present invention, that effective therapeutic activity over a period of 24 hours or more may be obtained from a morphine-containing sustained release formulation which gives an in vivo peak plasma level relatively early after administration, that is from 1.0 to 6 hours after administration preferably 1 to 4 hours eg 1 to 3.5 hours.

Accordingly, one embodiment of the composition of the invention provides an orally administrable sustained release dosage unit form containing morphine, or a pharmaceutically acceptable salt thereof, as active ingredient which formulation gives

a peak plasma level from 1 to 6 hours, after administration.

It has been found that in a group eg. n=5, of healthy volunteers such dosage units, when administered in a single dose in the fasted state, gave median t max values in the range of 1 to 4.25 hours.

When the morphine is administered as morphine sulphate and the method of plasma analysis is high performance liquid chromatography, the peak plasma level of morphine (per ml of plasma) is preferably from 0.5×10^{-7} to 7.5×10^{-7} times the amount of morphine sulphate orally administered. When morphine base or a salt other than the sulphate is administered, the preferred ratio of drug administered to peak plasma level should be adjusted according to the molecular weight of the base or salt.

The dosage unit form in accordance with the invention should contain sufficient morphine, or salt thereof, to give therapeutic activity over a period of at least 24 hours. The actual amount of morphine, or salt, in any particular dosage form will of course depend upon a number of variables including (i) the number of dosage forms intended to be administered at any one time and (ii) the intended dosage for any particular patient. Conveniently, however, dosage unit forms in accordance with the invention will contain from 10 to 500mg of morphine (calculated as morphine sulphate) and thus, for example, typical dosage unit forms in accordance with the invention are those containing 20, 30, 60, 90, 120, 150 and 200mg of morphine (calculated as above).

It has further been found, in accordance with the present invention, that in order to achieve the desired time of peak plasma level and to provide effective activity over a period of at least 24 hours, the in vitro release characteristics of the formulation [when measured by the modified Ph. Eur. Basket method at 100rpm in 900ml aqueous buffer

(pH 6.5) containing 0.05%w/v Polysorbate 80 at 37°C] are as set out below:

Hours after start of test	% Morphine (salt) released	
	suitable	preferred
2	5-30	5-20
4	15-50	15-35
6	20-60	20-45
12	35-75	40-70
18	45-100	50-80
24	55-100	60-100

The compositions of the invention may be provided in a variety of forms, for example as tablet or capsules containing granules, spheroids or pellets. Commonly, the composition will comprise the active ingredient (morphine or salt thereof) together with a diluent which may serve to modify the release of the active ingredient. A preferred form of unit dose form in accordance with the invention comprises a capsule filled with pellets essentially comprising the active ingredient, a hydrophobic fusible carrier or diluent and optionally a hydrophilic release modifier. In particular, the pellets are preferably prepared by a so-called "melt pelletisation" process. In essence, such process comprises forming a mixture of dry active ingredient and fusible release control materials followed by pelletising the mixture in a high speed mixer at a rate and energy input such that sufficient energy is supplied to the fusible material to melt or soften it whereby it forms pellets with the active ingredient. The resultant pellets, after cooling, are suitably sieved to give pellets having a particle size range from 0.1 to 3.0mm, preferably 0.25 to 2.0mm. A preferred and novel "melt pelletisation" process is described below which is suitable for the commercial production of dosage units containing morphine or other active substances.

When using such a processing technique it has been found that, in order to most readily achieve the desired release characteristics (both in vivo and in vitro as discussed above) the composition to be pelletised should comprise two essential ingredients namely:

- (a) active ingredient (morphine or salt thereof); and
- (b) hydrophobic fusible carrier or diluent; optionally together with
- (c) a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.

We have found that the total amount of active ingredient in the composition may vary within wide limits, for example from 10 to 60% by weight thereof.

The hydrophobic fusible component (b) should be a hydrophobic material such as a natural or synthetic wax or oil, for example hydrogenated vegetable oil or hydrogenated castor oil, and suitably has a melting point of from 35 to 100°C, preferably 45 to 90°C.

The release modifying component (c), when a water soluble fusible material, is conveniently a polyethylene glycol and, when a particulate material, is conveniently a pharmaceutically acceptable material such as dicalcium phosphate or lactose.

Incorporation of lower levels of morphine, for example between 10 and 30% by weight, necessitate inclusion of low levels of a release modifying component, for example 5 to 15% by weight polyethylene glycol 6000, to achieve a satisfactory in vitro release rate. At higher drug loadings, for example 40 to 60% by weight it is particularly surprising that only incorporation of very small amounts of polyethylene glycol, for example 0.01 to 1% by weight are required to modify the in vitro release rate.

Alternatively the morphine (or salt thereof) may be formulated (e.g. by dry or wet granulation or by blending) in a controlled release mixture formed of components other than fusible components. Suitable materials for inclusion in a controlled release matrix include, for example

- (a) Hydrophillic or hydrophobic polymers, such as gums, cellulose ethers, protein derived materials, nylon, acrylic resins, polylactic acid, polyvinylchloride, starches, polyvinylpyrrolidones, cellulose acetate phthalate. Of these polymers, cellulose ethers especially substituted cellulose ethers such as alkylcelluloses (such as ethylcellulose), C_1-C_6 hydroxyalkylcelluloses (such as hydroxypropylcellulose and especially hydroxyethyl cellulose) and acrylic resins (for example methacrylates such as methacrylic acid copolymers) are preferred. The controlled release matrix may conveniently contain between 1% and 80% (by weight) of hydrophillic or hydrophobic polymer.
- (b) Digestible, long chain (C_8-C_{50} , especially C_8-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, hydrogenated vegetable oils such as Cutina (Trade Mark), fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), glyceryl esters of fatty acids for example glyceryl esters of fatty acids for example glyceryl monostearate mineral oils and waxes (such as beeswax, glycowax, castor wax or carnauba wax). Hydrocarbons having a melting point of between 25°C and 90°C are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The matrix may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.
- (c) Polyalkylene glycols. The matrix may contain up to 60% (by weight) of at least one polyalkylene glycol.

A suitable matrix comprises one or more cellulose ethers or acrylic resins, one or more $C_{12}-C_{36}$, preferably $C_{14}-C_{22}$, aliphatic alcohols and/or one or more hydrogenated vegetable oils.

A particular suitable matrix comprises one or more alkylcelluloses, one or more C₁₂-C₃₆, (preferably C₁₄-C₂₂) aliphatic alcohols and optionally one or more polyalkylene glycols.

Preferably the matrix contains between 0.5% and 60%, especially between 1% and 50% (by weight) of the cellulose ether.

The acrylic resin is preferably a methacrylate such as methacrylic acid copolymer USNF Type A (Eudragit L, Trade Mark), Type B (Eudragit S, Trade Mark), Type C (Eudragit L 100-55, Trade Mark), Eudragit NE 30D, Eudragit E, Eudragit RL and Eudragit RS. Preferably the matrix contains between 0.5% and 60% by weight, preferably between 1% and 50% by weight of the acrylic resin.

In the absence of polyalkylene glycol, the matrix preferably contains between 1% and 40%, especially between 2% and 36% (by weight) of the aliphatic alcohol. When polyalkylene glycol is present in the oral dosage form, then the combined weight of the aliphatic alcohol and the polyalkylene glycol preferably constitutes between 2% and 40%, especially between 2 and 36% (by weight) of the matrix.

The polyalkylene glycol may be, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferably between 200 and 15000 especially between 400 and 12000. The morphine-containing controlled release matrix can readily be prepared by dispersing the active ingredient in the controlled release system using conventional pharmaceutical techniques such as melt granulation, wet granulation, dry blending, dry granulation or coprecipitation.

Another form of sustained release formulation comprises spheroids obtained by spheronizing the morphine (or salt thereof) with a spheronizing agent such as microcrystalline cellulose.

Patent Application PCT/SE93/00225 published under No. WO 93/18753 describes a process for the preparation of sustained release pellets which comprises pelletising a mixture containing the drug in finely divided form and a binder; the process is characterised in that:

- (a) the binder is in particle form consisting of one or more water-insoluble wax-like binder substance(s) with a melting point about 40°C and
- (b) the pelletisation step is performed by mechanically working the mixture, in a so-called high-shear mixer, under the input of a sufficient amount of energy for the binder to melt and pelletisation to take place.

We have found that by operating according to this method using commercial manufacturing equipment with a standard stainless steel interior, which is also the method described in Schaefer et al (*Drug Development and Industrial Pharmacy*, 16(8), 1249-1277 (1990) and Taggart et al (*International Journal of Pharmaceutics* 19 (1984) 139-148), results in yields of pellets in the preferred size range of only about 30 to 60% compared with the theoretical. Use of a wider particle size range to improve the yield results in an erratic in vitro release rate and irreproducible performance.

There is, therefore, a need for a commercial process for producing satisfactory controlled release pellets which has a much higher yield. Another object of the invention is, therefore, to provide a melt pelletisation method which has an improved yield and preferably produces a product with reproducible controlled release characteristics.

The present invention thus also includes a process for the manufacture of pellets, preferably sustained release pellets, which comprises

- (a) mechanically working in a high-speed mixer, a mixture of a particulate drug and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35 to 100°C and optionally a release control component comprising a

water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates;

- (b) breaking down the larger agglomerates to give controlled release seeds; and
- (c) continuing mechanically working with a further addition of low percentage of the carrier or diluent.

This process is capable of giving a high yield (over 80%) of pellets in a desired size range, with a desired in vitro release rate, uniformity of release rate and in its preferred form surprisingly an early peak plasma level for a product with 24 hour duration of activity.

The resulting pellets may be sieved to eliminate any over or undersized material then formed into the desired dosage units by for example, encapsulation into hard gelatin capsules containing the required dose of the active substance.

The drug may be water soluble or water insoluble. Water soluble drugs will usually be used in amounts giving a loading of up to about 50% w/w in the resulting pellets; water insoluble drugs may be used in higher amounts eg. up to 90% w/w of the resulting pellets; Examples of water soluble drugs which can be used in the method of the invention are morphine or its salts eg. the sulphate, hydromorphone, diltiazem and tramadol; examples of water insoluble drugs which can be used to the method of the inventions are naproxen, ibuprofen and indomethacin.

In a preferred method according to the invention morphine sulphate is used in an amount which results in pellets containing between 10% and 60%, especially between about 45% and about 60% w/w active ingredient for a high dose product and 10 and 45% for a low dose product.

In the method of the invention all the drug is added in step (a) together with a major portion of the hydrophobic fusible release control material used. Preferably the amount of fusible release control material added in step (a) is between 25% and 45% w/w of the total amount of ingredients added in the entire manufacturing operation, more preferably between 30% and 40%.

In step (c) the amount of additional fusible release control material added is preferably between 5% and 20% w/w of the total amount of ingredients added, more preferably between 8 and 17% w/w.

Stage (a) of the process may be carried out in conventional high speed mixers with a standard stainless steel interior, e.g. a Collette Vactron 75 or equivalent mixer. The mixture is processed until a bed temperature above 40°C is achieved and the resulting mixture acquires a cohesive granular texture, with particle sizes ranging from about 1-3 mm to fine powder in the case of non-aggregated original material. Such material, in the case of the embodiments described below, has the appearance of agglomerates which upon cooling below 40°C have structural integrity and resistance to crushing between the fingers. At this stage the agglomerates are of an irregular size, shape and appearance.

The agglomerates are preferably allowed to cool. The temperature to which it cools is not critical and a temperature in the range room temperature to 37°C may be conveniently used.

The agglomerates are broken down by any suitable means, which will comminute oversize agglomerates and produce a mixture of powder and small particles preferably with a diameter under 2mm. It is currently preferred to carry out the classification using a Jackson Crockatt granulator using a suitable sized mesh, or a Comil with an appropriate sized screen. We have found that if too small a mesh size is used in the aforementioned apparatus the agglomerates melting under the action of the beater or impeller will clog the mesh and prevent further throughput of mixture, thus reducing yield. A mesh size of 12 or greater or a 94G Comill screen have been found adequate.

The classified material is returned to the high speed mixer and processing continued. It is believed that this leads to cementation of the finer particles into pellets of uniform size range.

In a preferred form of the method of the invention processing of the classified materials is continued, until the hydrophobic fusible materials used begin to soften/melt and additional hydrophobic fusible material is then added. Mixing is continued until the mixture has been transformed into pellets of the desired predetermined size range.

In order to ensure uniform energy input into the ingredients in the high speed mixer it is preferred to supply at least part of the energy by means of microwave energy.

Energy may also be delivered through other means such as by a heating jacket or via the mixer impeller and chopper blades.

After the pellets have been formed they are cooled or allowed to cool, and may then be sieved to remove any over or undersized material.

The resulting pellets may be used to prepare dosage units such as tablets or capsules in manners known per se.

In order that the invention may be well understood the following examples are given by way of illustration only.

EXAMPLES

Pellets, having the formulations given in Table I below, were prepared by the steps of:-

- (i) placing the ingredients, in a total amount by weight of 10kg, in the bowl of a 75 litre capacity Collette Vactron Mixer (or equivalent), equipped with variable speed mixing and granulating blades;

- (ii) mixing the ingredients while applying heat until the contents of the bowl are pelletised;
- (iii) discharging the pellets from the mixer and sieving them to separate out the pellets collected between 0.5 and 2mm aperture sieves.

	TABLE I							
EXAMPLE NO.	1	2	3	4	5	6	7	8
Morphine Sulphate (wt%)	15	15	15	23	55	55	55	55
Hydrogenated castor oil U.S.N.F. (wt. %)	77	76	75	70	-	-	-	-
Hydrogenated vegetable oil U.S.N.F.(wt. %)	-	-	-	-	42.8	45	44.95	42.0
Polyethylene glycol 6000 U.S.N.F. (wt. %)	8	9	10	7	0.2	-	0.05	-
Dicalcium phosphate anhydrous USP (Wt. %)	-	-	-	-	2	-	-	3

The in vitro release rates of the products of Examples 1, 2, 3 and 5 were assessed by the modified Ph.Eur. Basket method at 100rpm in 900ml aqueous buffer (pH6.5) at 37°C. For each of the products, six samples of the pellets, each sample containing a total of 30mg of morphine sulphate, were tested. The results set out in Table II below give the mean values for each of the six samples tested.

TABLE II				
PRODUCT OF EXAMPLE				
Hours after start of test	1	2	3	5
(% morphine released)				
2	19	25	33	44
4	27	36	49	57
6	34	45	62	66
8	41	52	72	72
12	53	64	86	81
18	66	77	96	89
24	76	86	101	92

Pharmacokinetic studies in health human volunteers have indicated peak plasma levels of from 2.2 to 21.6 ng/ml of morphine at median times between 1.0 and 3.5 hours following administration of a single capsule containing pellets of Examples 1, 2, 3 or 5 in an amount sufficient to provide a morphine sulphate dose of 30mg.

Pellets, having the formulations given in Table III below, were prepared by the steps of:

- i) Placing the ingredients (a) to (c) (total batch weight 20kg) in the bowl of a 75 litre capacity Collette Vactron Mixer (or equivalent) equipped with variable speed mixing and granulating blades;
- ii) Mixing the ingredients at about 150-350rpm whilst applying heat until the contents of the bowl are agglomerated.

- iii) Classifying the agglomerated material by passage through a Comill and/or Jackson Crockatt to obtain controlled release seeds.
- iv) Warming and mixing the classified material in the bowl of a 75 litre Collette Vactron, with addition of ingredient (d), until uniform pellets of the desired pre-determined size range are formed in yield of greater than 80%. This takes approximately 5 minutes.
- v) Discharging the pellets from the mixer and sieving them to separate out the pellets collected between 0.5 and 2mm aperture sieves.

TABLE III				
EXAMPLE	9	10	11	12
a) MORPHINE SULPHATE (WT%)	55.0	52.19	53.48	53.48
b) HYDROGENATED VEGETABLE OIL USNF (WT%)	34.95	33.17	33.98	33.98
c) POLYETHYLENE GLYCOL 6000 USNF (WT%)	0.05	0.047	0.049	0.049
d) HYDROGENATED VEGETABLE OIL USNF (WT%)	10.0	14.60	12.49	12.49
YIELD %	90.5	83.4	90.1	82.5

The in vitro release rates of Examples 9, 10, 11 and 12 were assessed by modified Ph. Eur Basket method at 100 rpm in 900ml aqueous buffer (pH 6.5) containing 0.05% w/v polysorbate 80 at 37°C. For each of the products, six samples of the pellets, each sample containing a total of 60mg of morphine sulphate were tested. The results set out in Table IV below give the mean values for each of the six samples tested.

TABLE IV PRODUCT OF EXAMPLES				
HOURS AFTER START OF TEST	9	10	11	12
	% MORPHINE RELEASED			
2	21	15	20	15
4	33	25	36	24
6	43	35	49	30
8	52	43	59	36
12	62	57	72	46
18	74	71	82	57
24	82	81	86	65
30	83	85	89	71

Pellets produced according to Examples 9 to 12 were each blended with purified talc and magnesium stearate and used to fill hard gelatin capsules such that each capsule contains 60mg of morphine sulphate. The capsules produced were used in open, randomised crossover studies. As part of these studies patients received after overnight fasting either one capsule according to the invention or one MST CONTINUS^R tablet 30mg (a twice a day preparation). Fluid intake was unrestricted from 4 hours after dosing. A low-fat lunch was provided four hours after dosing, a dinner at 10 hours post dose and a snack at 13.5 hours post-dose. No other food was allowed until a 24 hour post-dose blood sample had been withdrawn. Blood samples were taken at the following times 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12, 18, 24, 36, 48 and 72 hours post-dose.

The pharmacokinetic studies using these capsules gave peak plasma levels of from 3.2 to 29.2 ng/ml of morphine at median times between 2 and 6 hours following administration and blood sampling according to the above protocol.

The capsules containing pellets produced according to Examples 10 and 12 in particular gave a mean C_{max} of 11.9 ng/ml at median t_{max} 4 hours and mean C_{max} of 9.2 ng/ml at median t_{max} 2.5 hours respectively (these values represent the mean of the individual (C_{max} and t_{max} values). In contrast the C_{max} and t_{max} for the patients who received MST CONTINUS^R were 10.6 -11.4 ng/ml and 2.0 -2.5 hours respectively. It was found, however, that the plasma concentrations of morphine in the blood of patients given capsules according to the invention at 24 hours were greater than the concentrations at 12 hours in these patients given MST CONTINUS.

CLAIMS:

1. An orally administrable sustained release dosage unit form containing morphine, or a pharmaceutically ^{acceptable} salt thereof, as active ingredient, which composition gives a peak plasma level at 1.0 to 6 hours after administration.
2. A pharmaceutical composition as claimed in claim 1 containing from 10 to 500mg of morphine (calculated as morphine sulphate).
3. A pharmaceutical composition as claimed in claim 1 or claim 2 having in vitro release characteristics such that the formulation (when assessed by the modified Ph.Eur. Basket Method at 100rpm in 900ml aqueous buffer, (pH 6.5), containing 0.05% polysorbate at 37°C), releases from 5 to 30% of active ingredient two hours after start of test, 15 to 50% at 4 hours after start of test; 20% to 60% at 6 hours after start of test; 35 to 75% at 12 hours after start of test, from 45 to 100% at 18 hours after start test and 55 to 100% at 24 hours after start of test.
4. A pharmaceutical composition as claimed in any one of the preceding claims comprising a capsule filled with pellets essentially comprising the active ingredient and a hydrophobic release control material.
5. A pharmaceutical composition as claimed in claim 4 which has been prepared by a melt pelletisation process.
6. A pharmaceutical composition as claimed in claim 4 or claim 5 also containing from 0.01 to 20% by weight, based on the total weight of the pellets, of a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.
7. A pharmaceutical composition as claimed in claim 1 substantially as hereinbefore described with reference to the Examples.

8. A process for the manufacture of pellets, preferably sustained release pellets, which comprises
 - (a) mechanically working in a high-speed mixer, a mixture of a particulate drug and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35 to 100°C and optionally a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften whereby it forms agglomerates;
 - (b) breaking down the agglomerates to give controlled release seeds;
 - (c) continuing mechanically working with the addition of a low percentage of the carrier or diluent
9. A process according to claim 8, wherein during the mechanical working, heat is supplied thereto by microwave radiation.
10. A process according to claim 9, wherein only part of the heating is supplied by microwave radiation.
11. A process according to any one of claims 8 to 10, wherein the drug is morphine or a salt thereof.
12. A process according to any one of claims 8 to 11, wherein the hydrophobic fusible carrier(s) or diluent(s) is a hydrogenated vegetable oil.
13. A process according to any one of claims 8 to 12, wherein the water-soluble fusible material included in the mixture in step (a) is PEG 6000.

Patents 1977

Examiner's report to the Comptroller under Section 17
(The Search report)Application number
GB 9324045.5

Relevant Technical Fields

- (i) UK Cl (Ed.M) A5B (BLM)
(ii) Int Cl (Ed.5) A61K 9/16, 9/52

Search Examiner
J F JENKINSDate of completion of Search
10 FEBRUARY 1994

Databases (see below)

(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE DATABASES: DIALINDEX (MEDICINE), WPI, CAS-ONLINE

Documents considered relevant following a search in respect of Claims :-
1-7

Categories of documents

- X:** Document indicating lack of novelty or of inventive step. **P:** Document published on or after the declared priority date but before the filing date of the present application.
- Y:** Document indicating lack of inventive step if combined with one or more other documents of the same category. **E:** Patent document published on or after, but with priority date earlier than, the filing date of the present application.
- A:** Document indicating technological background and/or state of the art. **&:** Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
X	EP 0377518 A2 (F H FAULING & CO) See page 9 lines 8-27 and Examples	1-4
Y	EP 0271193 A2 (EUROCELTIQUE) Whole document	1-4 and 6
Y	EP 0108218 A2 (VEREX LABS) See page 7 line 27	1-4 and 6
X	WO 92/02209 A1 (AIACHE) See Examples 1, 2 and 7	1-4
Y	WO 92/01446 A1 (APS RESEARCH) See page 2 line 26 - page 3 line 2	1-6
Y	US 3634584 (AMERICAN HOME PRODUCTS) See column 4 line 58	1-4 and 6
X	Curr Ther Res 47, pages 869-878 (1990) R F KAIKO ET AL	1-4
A	British National Formulary No 25 (March 1993), page 181 - see MST-Continus	1

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).

Relevant Technical Fields

- (i) UK Cl (Ed.M) A5B (BLL, BLM, BNC)
 (ii) Int Cl (Ed.5) A61K 9/16

Search Examiner
 J F JENKINS

Date of completion of Search
 23 JUNE 1994

Databases (see below)

(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE DATABASE: WPI

Documents considered relevant following a search in respect of Claims :-
 8 TO 13

Categories of documents

- X:** Document indicating lack of novelty or of inventive step. **P:** Document published on or after the declared priority date but before the filing date of the present application.
- Y:** Document indicating lack of inventive step if combined with one or more other documents of the same category. **E:** Patent document published on or after, but with priority date earlier than, the filing date of the present application.
- A:** Document indicating technological background and/or state of the art. **&:** Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
A	WO 93/18753 A1 (KABI PHARMACIA) see Examples 5 and 6; Claim 3	
A	WO 92/06679 A1 (KABI PHARMACIA) see Claim 1	
A	US 4132753 (BLICHARE et al) see Claim 1	

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